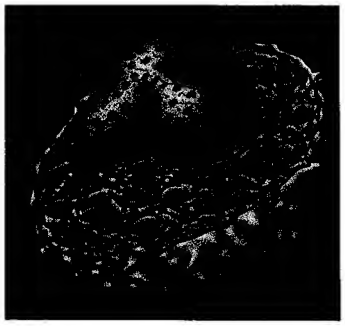
Molecular Cell Biology

SECOND EDITION



JAMES DARNELL
Vincent Astor Professor
Rockefeller University

▲

HARVEY LODISH
Member of the Whitehead Institute for Biomedical Research
Professor of Biology, Massachusetts Institute of Technology

▲

DAVID BALTIMORE
President (designate)
Rockefeller University

SCIENTIFIC AMERICAN BOOKS
Distributed by W. H. Freeman and Company, New York

Cover illustration by Tomo Narashima

Library of Congress Cataloging-in-Publication Data

Darnell, James E.
Molecular cell biology / James Darnell, Harvey Lodish, David Baltimore.—2d ed.
p. cm.
Includes bibliographical references.
ISBN 0-7167-1981-9:—ISBN 0-7167-2078-9 (international student ed.):
1. Cytology. 2. Molecular biology. I. Lodish, Harvey F. II. Baltimore, David. III. Title.
[DNLM: 1. Cells. 2. Molecular Biology. QH 581.2 D223m]
QH581.2.D37 1990
574.87'6042—dc20
DNLM/DLC
for Library of Congress 89-70096
CIP

Printed in the United States of America

Scientific American Books is a subsidiary of Scientific American, Inc.
Distributed by W. H. Freeman and Company, 41 Madison Avenue, New York, New York 10010 and 20 Beaumont Street, Oxford OX1 2NQ England

1 2 3 4 5 6 7 8 9 0 KP 9 9 8 7 6 5 4 3 2 1 0

cells treated with protease exhibit some characteristics of transformation (loss of actin microfilaments, growth stimulation, etc.), suggesting that plasminogen activator secretion may help maintain the transformed state of certain cell lines.

Secretion of plasminogen activator by transformed cells may be related to their tumor-forming capacity because the resulting increase in plasmin may help the cells penetrate the basal lamina. The normally invasive extraembryonic cells of the fetus secrete plasminogen activator when they are implanting in the uterine wall; this provides a compelling analogy to invasion by tumor cells. Whether plasminogen activator acts only by cleaving circulating plasminogen or whether it can attack other proteins directly is an open question.

Altered Gene Transcription All of the foregoing characteristics of transformed cells are cytoplasmic activities; yet it might be expected that the extraordinary range of differences between normal and transformed cells would be at least partly due to alterations in the transcription of specific genes and in the relative stability of the transcripts. Surprisingly, however, the mRNA populations of normal cells and transformants derived from them are quite similar. The concentrations of some mRNAs are increased and those of some are decreased, but only about 3 percent of the total mRNA is specific to transformed cells. The transformation-specific mRNA probably includes many different low-abundance species. The proteins translated from these mRNAs, although low in concentration, have profound effects on cell growth and morphology. Some transformation-specific mRNAs also appear in embryonic cells, and tumor cells have many proteins that are characteristic of embryonic cells; this would suggest that transformation may alter protein composition toward that characteristic of embryos.

Immortalization of Cell Strains When cell strains, with their limited growth potential in culture, are used as targets for cell transformation, then one measurable characteristic of transformation is the induction of unlimited growth potential—that is, the conversion of a cell strain into an immortal cell line. (Obviously, immortalization cannot be used as an indicator of transformation in cell lines because they are immortal before exposure to transforming stimuli.) The ease with which transforming stimuli can generate immortal cell lines from cell strains depends on the underlying propensity of the cells to spontaneously acquire immortality: nonadherent (blood) cells from many animals are routinely immortalized by transformation; adherent human cells are rarely immortalized. Adherent chicken cells are almost never immortalized, but adherent rodent cells are easily transformed to immortality. The other characteristics of transformation described above are as relevant to adherent human and chicken cells as they are to mouse cells, which implies that immortalization is quite distinct from other transformation parameters.

Transcription of Oncogenes Can Trigger Transformation

The differences in the properties of normal cultured cells and their transformants, summarized in the previous section, provide only limited clues to the mechanism or cause of transformation. Although the key steps in transformation and the interrelationship between various transformation parameters are still largely matters of conjecture, it is known that the events triggering transformation can be comparatively simple, often resulting from the transcription of one or two genes. These genes—now called oncogenes—may be part of a virus, or they may be altered cellular genes. An *oncogene* is a gene whose product is involved either in transforming cells in culture or in inducing cancer in animals; many oncogenes also are believed to play important roles in human cancer. (The word *oncogene* derives from the Greek *onkos,* meaning a bulk or mass; *oncology* is the scientific study of tumors.)

Of the many oncogenes known, all but a few are derivatives of certain normal cellular genes. Such genes (or *proto-oncogenes*) are important for normal cellular processes but can be altered, often in very simple ways, to become oncogenes. The normal genome of some DNA viruses also contain oncogenes, which both help the virus grow and can transform cells or induce cancer. Oncogenes are named with three-letter italic designations (e.g., *src*). Because most proto-oncogenes are basic to animal life, they have been highly conserved over eons of evolutionary time. Many are evident in the DNA of arthropods (like *Drosophila*), and some are even found in yeast.

As noted earlier, three types of transforming agents are known: viruses, chemicals, and radiation. These agents were recognized as carcinogens in animals before their ability to transform cultured cells was discovered. In the next several sections, we describe the role of each of these agents in transformation and/or carcinogenesis and their relationship to oncogenes. Following this, we will consider the role that proto-oncogenes and oncogenes play in the metabolism of normal cells and cancer cells.

DNA Viruses as Transforming Agents

Some animal viruses have RNA and some have DNA as their genetic material (see Table 5-4). One group of RNA viruses, the *retroviruses,* and many types of DNA viruses